UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,571	06/26/2003	Richard P. Batycky	2685.2046-003	6287

38421 7590 09/09/2005

ELMORE CRAIG & VANSTONE, P.C.
209 MAIN STREET
N. CHELMSFORD, MA 01863

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/607,571	BATYCKY ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *140-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *140-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/12/04 & 6/26/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-139 have been cancelled. Claims 140-173 are pending.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 146-150 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "substantially amorphous or substantially crystalline" in claims 146-150 are relative terms which render the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is noted that Applicant defines the term "substantially anti-oxidant free" on page 24 of the specification as having a quantity of anti-oxidant that is less than about 2 percent. However, the intended definition implied by the use of the term "substantially" to modify the accepted meaning of the words "amorphous" and "crystalline" in claims 146-150 is not defined. As a result, the intended limitations of the phrases "substantially amorphous" and "substantially crystalline" is unclear. A person of ordinary skill in the art would not be able to interpret

unambiguously the intended meaning of the phrases "substantially amorphous" and "substantially crystalline" based on the content of Applicant's disclosure.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 140, 145-147, 149, 151, 156-158, 160, 163-168, 170 and 171 are rejected under 35 U.S.C. 102(b) as being anticipated by Radhakrishnan (U.S. patent 5,049, 389).

Applicant's claims are drawn to a method of treating a patient in need of epinephrine comprising administration to the patient's respiratory system of particles comprising (a) epinephrine, or a salt thereof and (b) at least one pharmaceutically acceptable excipient wherein (i) the particles posses a fine particle fraction of less than 5.6 μm of at least about 45 percent; (ii) the particles are spray dried; (iii) both epinephrine and the excipient are substantially amorphous; (iv) a first portion of the particles is deposited in the upper airways of the respiratory system and a second portion is deposited in the alveoli region of the lungs; (v) the epinephrine released from the particles acts locally; and (vi) the drug is released from the particles in a sustained manner.

Radhakrishnan discloses a method for treating a patient in need of epinephrine by administration of particles comprising a nonphospholipid composition consisting essentially of nonphospholipid components and a drug (adrenaline) aerosolized into aerosol particles having a **mass median aerodynamic diameter smaller than 2.1 μm** and providing a **slow or sustained release of the drug in the lungs** (claims 13 and 15). Adrenaline is also called epinephrine (c.f. The Physicians' Desk Reference, Medical Economic Company: Montvale, NJ, 2002, p 2233). Fine particle fraction (FPF) is defined by Maa et al. as "powder with an aerodynamic mass

median diameter (MMAD) of less than 6.8 μm. Radhakrishnan's particles meet the limitations of claim 140 requiring a FPF of less than 5.6 μm of about 45%, because the average MMAD of these particles is 2.1 μm.

Radhakrishnan discloses that the dried particle liposome formulation in the form of dry powder can be prepared either by lyophilization or **spray drying**. For spray drying, the particle suspension is dried in a conventional apparatus in which the particles to be dried are sprayed in aerosolized suspension form into a stream of heated air or inert gas, and the aerosolized droplets are dried in the gas stream as they are carried toward a dry powder collector (column 14, lines 22-23 and lines 28-32).

Radhakrishnan discloses that because of the unique, cholesteryl sulfate formulations which accommodates the drug by stearic fit, and because of their high encapsulation and high retention values, **drug crystallization does not occur outside or inside the liposomes**, nor does sedimentation occur from the suspension (column 13, lines 62-67).

Radhakrishnan discloses that the method of treating a patient is by the **inhalation route of administration** to a person in need of such treatment (claims 13, 18, and 20).

Radhakrishnan discloses that portions of the drug are delivered to a patient's respiratory system including **the upper airways and the alveolar regions** (see Figure 3 and column 19, lines 8-13).

Radhakrishnan discloses that the administered drug provides increased and extended **local therapeutic effect in the lungs**. The drug incorporated in the particles may be adrenaline, which is also called epinephrine (column 19, lines17-18 and column 20, lines 25-30).

Claims 163 and 167 require the administration of the particles of claim 140. The coefficient of variation for the maximum epinephrine concentration, C_{max}, in a patient's blood plasma of a dose of epinephrine and the associated T_{max} are inherent characteristics of the administration of said particles to a patient and these quantities (C_{max} and T_{max}) also would inherently be better than what one would expect from a non-intravenous injection of epinephrine.

The justification for the rejection of claims 164-166,168, and 170 are related to the reasoning used to reject claims 163 and 167. The ability of the particles to induce a higher maximum epinephrine blood plasma concentration in a shorter period of time (i.e. lower T_{max}) than that resulting from the non-intravenous injection of epinephrine or the administration of a liquid-based aerosol is an inherent characteristic of the administration of these particles, as would be appreciated by a skilled person in the art.

Secondary references were used in this 102 rejection. This is permissible according to the MPEP § 2131.01, when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"

(B) Explain the meaning of a term used in the primary reference; or

(C) Show that a characteristic not disclosed in the reference is inherent.

In the instant rejection the extra references were used to define Fine Particle Fraction (condition B) and show that the term "adrenaline" is synonymous with "epinephrine" (condition A).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 140, 145-147, 149, 151, 156-158, 160, 163-168, 170 and 171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radhakrishnan (U.S. patent 5,049, 389) as applied above.

The above 102 rejection was based upon the administration of particles comprising epinephrine and at least one pharmaceutically acceptable excipient wherein the particles had a fine particle fraction of less than 5.6 μm of at least about 45 percent. It was assumed that Radhakrishnan's particles, having a mass median aerodynamic diameter smaller than 2.1 μm, inherently met the limitation of particles having a FPF of less than 5.6 μm of at least about 45%. The assumption was based upon the argument that a MMAD of 2.1 μm is sufficiently smaller than 5.6 μm that a mathematical analysis of said particles would show that at least about 45% of these particles had a FPF of less than 5.6 μm.

If Applicant is able to show that Radhakrishnan's particles do not inherently meet the limitation of having a FPF of less than 5.6 μm of at least about 45% and the above 102(b) rejection does not hold, then it would have been obvious to a person of ordinary skill in the art to modify the FPF of Radhakrishnan's particles to meet this limitation. An artisan would have been

motivated at the time of the instant invention to optimize the FPF of particles comprising epinephrine to improve the penetration of these particles in the respiratory system when administered by inhalation and therefore the efficacy of treatment upon administration of said particles.

Claims 140-145, 151, 154-158, 161-168, 170, and 171 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maa et al. (U. S. patent 6,284,282) in view of the 56th edition (2002) of the Physicians' Desk Reference (PDR, page 1236).

Applicant's claims are drawn to a method of treating a patient in need of epinephrine comprising administration to the patient's respiratory system of particles comprising (a) epinephrine, or a salt thereof and (b) at least one pharmaceutically acceptable excipient wherein (i) the particles posses a fine particle fraction of less than 5.6 μm of at least about 45 percent; (ii) the particles are spray dried; (iii) both epinephrine and the excipient are substantially amorphous; (iv) the particles are aerodynamically light; (v) a first portion of the particles is deposited in the upper airways of the respiratory system and a second portion is deposited in the alveoli region of the lungs; (vi) the epinephrine released from the particles acts locally; (vii) a first portion is deposited in the airways of the respiratory system and a 2nd portion is deposited in the alveoli region of the lungs; (viii) the particles are administered via inhalation; (ix) the particles are delivered to the respiratory system via a breath activated inhaler; (x) the particles are administered to the respiratory system in a single breath activated step; (xi) the patient in need of epinephrine is suffering from anaphylaxis; (xii) the patient in need of epinephrine exhibits at least one condition selected from the group consisting of bronchoconstriction,

bronchospasm, airway constriction, and edema, or (xiii) the drug is released from the particles in a sustained manner.

Maa et al. teaches methods and compositions comprising spray freeze-dried formulations of therapeutic proteins, that show good dispersibility and respirable properties, as well as good stability (column 3, lines 53-56).

Maa teaches the desirability of having **aerodynamically light** particles is that said particles are likely to travel with air streamlines and reach deep in the lung for effective deposition (column 4, lines 44-48).

Maa teaches that spray freeze-drying is a process conceptually similar to spray drying, in that a homogeneous aqueous mixture is introduced via a nozzle (e.g. a two-fluid nozzle), spinning disk or an equivalent device into a cold fluid to atomize the solution to form fine droplets (column 5, lines 8-14).

Maa teaches that The spray freeze dried powders of the invention may be characterized on the basis of a number of parameters, including, but not limited to, the average particle size, the range of particle sizes, the **fine powder fraction (FPF),** the average particle density, and the mass median aerodynamic diameter (MMAD). The FPF is a measure of the aerosol performance of a powder, with the higher the fraction, the better. The FPF is defined as powder with an aerodynamic mass median diameter of less than 6.8 μm as determined using a multiple-stage liquid impinger with a glass throat (MLSI, Astra, Copley Instrument, Nottingham, UK) through a dry powder inhaler (Dryhalter™, Dura Pharmaceuticals) (see FIG. 5 and column 5, lines 42-46 and 59-65). See also column 18, lines 23-26 and Tables 3 and 4.

Maa teaches that the spray freeze-dried compositions may contain **excipients**, including **leucine** (column 8, lines 7-32).

Maa teaches the quantity of excipients used in the formulations can range from **1 to 95 wt%**, with the remainder of a formulation's composition comprising the active drug and other components (column 8, lines 35-39).

Maa teaches that the powders of the invention can be formulated **with other drugs** with the combination of drugs used depending on the disorders for which the drugs are given (column 10, lines 55-56 and 60-62).

Maa teaches that the powders may contain other additives, including preservatives, detergents, surfactants, antioxidants, bulking agents, water, buffers or solvents, salts, and other additives/generally known in the art (column 9, lines 40-41, column 11, lines 15-17, and column 12, lines 51-52).

Maa teaches that the powders can be readily dispersed by an **inhalation device** and subsequently **inhaled** by a patient so that the particles are able to penetrate into the **alveolar regions** of the lungs of the patient (column 12, lines 53-56).

In order to penetrate into the alveolar regions of the lungs of the patient, the particles must pass first through the upper airways of the respiratory system, of which the alveoli and lungs are a part. The term "portion" in claims 156-158 is understood to refer to any part or share of the inhaled formulation, however large or small, per the definition in the 2002 *Oxford American Dictionary of Current English* on page 614).

Maa teaches that the therapeutic protein is suitably administered to the patient **at one time** or over a series of treatments and may be administered to the patient at any time from diagnosis onwards (column 13, lines 12-13).

Maa teaches that the pharmaceutical formulations may be contained within unit dosage containers associated with **inhalers** that will deliver the powder to the patient. These inhalers may optionally have chambers into which the powder is dispersed, suitable for **inhalation by a patient** (column 13, lines 26-30).

Inhalation is defined in the 2002 *Oxford American Dictionary of Current English* on page 405 as an act of breathing in air. An inhaler is defined on the same page as a portable device used for relieving especially asthma by inhaling. Therefore, the term "breath activated inhaler" is redundant since to inhale is "to breathe in" and an inhaler requires inhalation.

The powder compositions of Maa's invention may be further formulated in other ways, for example, in the preparation of **sustained release compositions**. Sustained-release compositions also include liposomally entrapped proteins (column 13, lines 31-34 and 46-58).

Disorders benefiting from the administration of Maa's therapeutic protein include lung diseases among others (column 14, lines 14-59).

Maa lacks the teaching of formulations containing epinephrine and the administration of said formulations to a patient suffering from anaphylaxis and exhibiting at least one of the following conditions: bronchoconstriction, bronchospasm, airway constriction, and edema.

The 2002 PDR teaches on page 1236 that **epinephrine is essential in the treatment of anaphylaxis** (1st sentence in the section entitled "Precautions"). It also teaches in the "Clinical Pharmacology" section that epinephrine acts to relieve vasodilation and increased vascular

permeability. It also **relaxes the bronchial smooth muscles**, which alleviates wheezing and dyspnea. Other conditions alleviated by administration of epinephrine are pruritis, urticaria, and **angioedema** and it may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

It would have been obvious to a person of ordinary skill in the art at the time of the present invention to modify Maa 's powder formulations to include epinephrine as one of the other drugs that could be made according to Maa's invention for several reasons. It was taught that Maa's invention could be used to treat lung diseases. The bronchioles and the lungs are both part of the respiratory system and administration of epinephrine can induce the relaxation of bronchial smooth muscles to alleviate wheezing and other conditions involving the respiratory system. Maa's powdered formulations have the appropriate fine particle fraction and particle sizes required for these respirable pharmaceutical preparations to penetrate deep into the alveolar region of the lungs and act locally. In addition, Maa's invention can be administered to a patient upon inhalation from an inhaler. A skilled artisan would have had a reasonable expectation of successfully using Maa's formulations modified to include epinephrine to treat a patient suffering from anaphylaxis or bronchoconstriction, because it is accepted in the art that epinephrine is essential in the treatment of anaphylaxis and epinephrine is known cause the relaxation of bronchial smooth muscles, which would alleviate bronchoconstriction. It would have been obvious to a person of ordinary skill in the art, upon monitoring a patient's progress, that the administration of the respirable particles of the instant invention would lead to higher maximum blood serum levels in a shorter period of time than what would have been observed

had epinephrine been administered via a non-intravenous injection or using a liquid-based aerosol.

Claim 148 and 149 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maa in view of the 56th edition of the Physicians' Desk Reference as applied to claims 140-145, 151, 154-158, 161-168, 170, and 171 above, and further in view of Jakupovic et al. (U.S. patent 6,221,398).

Maa and the PDR lack in teaching a method of administering particular compositions comprising epinephrine (i.e. adrenaline) and a pharmaceutically acceptable excipient to the respiratory system, wherein the epinephrine and/or the pharmaceutically acceptable excipient are "substantially" crystalline.

Jakupovic et al. teach a method of preparing pharmaceutical powders for inhalation, wherein the powder comprises **crystalline particles of an inhalation compound**, in particular particles of mass median diameter 10 μm or less (column 1, lines 8-11).

Jakupovic teaches the desirability that the powder consists of particles in which at least 90% have a diameter of 10 μm or less. These powder compositions can be administered orally or nasally (column 2, lines 50-56).

Jakupovic teaches that through his invention it is possible to control the size of the particles obtained by controlling any or all of the parameters such as concentration of the compound in the solvent, the rate of addition of the solution into an antisolvent, and the agitation intensity, such that particles within a specified size range may be obtained (column 2, lines 66-67 and column 3, lines 1-7).

Jakupovic teaches that medically useful compounds may be provided in respirable particle form according to his invention, including **adrenaline (i.e. epinephrine)** (column 3, lines 8-32).

Jakupovic's compositions may also comprise pharmaceutically acceptable additives, including carriers, diluents, penetration enhancers, etc. (column 3, lines 43-57).

Jakupovic teaches that the precipitated compound may be dried in a conventional manner, for example it may be spray-dried, and may be agglomerated and/or spheronized if desired. No conditioning is necessary as the particles obtained are considered to be **completely crystalline**. Jakupovic also describes methods of monitoring the crystallinity of the respirable particles (column 4, lines 38-43 and 55-63).

A person of ordinary skill in the art at the time of the instant invention would have been motivated to combine the teachings of Maa, the PDR, and Jakupovic, in order to obtain crystalline respirable particles that could be administered to a patient. An artisan would have been motivated to combine these teachings because both Maa and Jakupovic teach therapeutic compositions intended for administration via inhalation in which the desired particle size can be controlled. Maa teaches that other drugs in addition to therapeutic proteins can be incorporated into the formulations he teaches, whereas Jakupovic teaches the administration of adrenaline, also called epinephrine. A person of ordinary skill in the art would have had a reasonable expectation of successfully obtaining "substantially" crystalline particles for therapeutic administration using the invention of Jakupovic, because this invention leads to particles that are considered to be **completely crystalline**.

Claim 152, 153, 159, and 169 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maa in view of the 56th edition of the Physicians' Desk Reference as applied to claims 140-145, 151, 154-158, 161-168, 170, and 171 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.*, 1986, *40(6)*, 673-678).

Maa and the PDR lack data on parameters evaluating adrenaline blood serum levels (e.g. C_{max}, T_{max}, dosages).

Warren et al. teach that inhalation of 30 puffs of adrenaline (3 mg) from a pressurized aerosol resulted in peak blood plasma levels of adrenaline (C_{max}) of **4.22 ± 1.93 nM after 1 minute (T_{max}) of administration**. They compared these results to adrenaline administered by a subcutaneous injection, which resulted in peak blood plasma levels of adrenaline (C_{max}) of 2.43 ± 0.47 nM after 10 minutes (T_{max}) of administration. The blood plasma levels of adrenaline were used as a measure of the systemic absorption of adrenaline (abstract, Figures 1 and 3 on pages 674 and 675, respectively).

A person of ordinary skill in the art at the time of the instant invention would have been able to obtain information on Warren et al.'s studies showing that the administration of inhaled adrenaline would lead to a shorter time for adrenaline blood plasma levels to reach a maximum concentration. A skilled artisan would have known that drug blood plasma levels are a measure of the systemic absorption of a pharmaceutical agent and that said agent would therefore be acting systemically. Based on Warren's data, a person of ordinary skill in the art at the time of the instant invention would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that said drug administered by inhalation would result in maximum adrenaline blood serum levels in the shortest period of time.

Claims 172 and 173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maa as applied to claims 140-145, 151, 154-158, 161-168, 170, and 171 above, and further in view of Adjei et al. (U.S. patent 6,136,294) and Dobrozsi (U.S. patent application PG-PUB, 2002/0076421).

Maa lacks the explicit teaching of using formulations comprising epinephrine bitartrate and sodium tartrate.

Adjei et al. teach amino acid stabilized medical aerosol formulations comprising (1) a particulate medicament or drug, (2) a suitable propellant, and (3) a suitable stabilizer. The particulate medicament or drug must be suitable for **inhalation** and belong to at least one of several therapeutic categories of pharmaceuticals, including **bronchodilators**. Particular suitable medicaments include **epinephrine**. Also included are the suitable **acid addition salts** of these drugs, their hydrates, and their solvates. Suitable acid addition salts include the salts obtained from inorganic acids, as well as organic acids such as **tartaric acid**, etc (column 2, lines 9-39).

Adjei teaches that the particles have a preferred size of **less than 5 microns**, in order that the particles can be inhaled into the **respiratory tract and/or lungs** (column 2, lines 46-47).

Adjei teaches that the particulate medicament or drug is present in the inventive formulations in a therapeutically effective amount, such that the drug can be administered as an aerosol (topically or via **oral or nasal inhalation**) and cause its desired therapeutic effect, typically **preferred with one dose**, or through several doses. The particulate drug is administered as an aerosol from a conventional valve, e.g., a metered dose valve (column 2, lines 48-54).

Adjei teaches that the stabilizer is an amino acid, including leucine. Generally, the stabilizer can be present in the formulation in amount from 0.000002 weight percent to 20 weight percent (column 3, lines 15-50) and column 4, lines 5-7).

Adjei teaches that the formulation of the invention can be delivered to the respiratory tract and/or lung by oral inhalation in order **to effect bronchodilation** or in order to treat a condition susceptible of treatment by **inhalation**, e.g., **asthma, chronic obstructive pulmonary** disease. The formulations of the invention can also be delivered by nasal inhalation in order to treat, e.g., allergic rhinitis, rhinitis, (local) or diabetes (systemic), or they can be delivered via topical (e.g., buccal) administration in order to treat, e.g., angina or local infection (column 4, lines 63-67 and column 5, lines 1-5).

Adjei teaches that aerosol canisters containing said formulation can deliver the formulations of the invention, including metered dose valves (column 4, lines 37-39).

Dobrozsi teaches mucoretentive pharmaceutical aqueous liquid compositions comprising about 2% to about 50% by weight of colloidal particles and a safe effective amount of a pharmaceutical active agent selected from a group including bronchodilators. Dobrozsi also teaches methods of treating or preventing **symptoms of upper respiratory tract infections or upper respiratory tract tissue irritation or damage** as well, by administering safe and effective amounts of the above-mentioned compositions (paragraphs 0009-0012).

Dobrozsi teaches that the active agents of the invention may include **bronchodilators** present in the composition in quantities ranging from about **0.01 wt. % to about 50 wt. %** (paragraph 0057). Included in the bronchodilators that may be used as an active agent is **epinephrine** (paragraph 0067).

Dobrozsi states that the compositions of the present invention may optionally contain pharmaceutically acceptable excipients from about 0.005% to about 3% of a substituted or unsubstituted, short chain, (C_1 to C_6), alkyl or aryl carboxylic acid including tartaric acid and salts thereof (paragraph 0107).

Dobrozsi state that the desired isotonicity of the intranasal compositions of this invention may be accomplished using, for example, sodium tartrate or other inorganic or organic solutes or mixtures thereof (paragraph 0119).

A person of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Maa, Adjei, and Dobrozsi, because all these inventors teach pharmaceutical formulations that can be inhaled to administer therapeutic agents to the respiratory system and treat symptoms and conditions associated with the respiratory system (e.g. lung diseases, asthma, COPD, and to affect bronchodilation.). Maa and Adjei both teach compositions containing leucine. Maa teaches that the quantity of leucine, used to stabilize therapeutic proteins, may range from 1 to 95 weight %. This range is inclusive of the range applicant cites in claim 172. Adjei provides additional motivation for the use of leucine, as it can be used to stabilize other medicaments (e.g. epinephrine) in addition to the therapeutic agents taught by Maa. Adjei teaches a range of quantities of leucine that are encompassed by the ranges taught by Maa. A skilled artisan would have known from the teachings of Adjei that the acid addition salts of different bronchodilators, including **epinephrine**, can be used to make pharmaceutically acceptable respirable particles. **Epinephrine bitartrate** is an acid addition salt derived from epinephrine and tartaric acid (a dicarboxylic organic acid). A person of ordinary skill in the art would have been motivated to use the appropriate epinephrine salt to optimize the

medical efficacy of pharmaceutically acceptable respirable particles. The use of a salt is an example of how a person of ordinary skill in the art could optimize a given formulation to maximize its utility. A skilled person in the art would also have been motivated to include sodium tartrate in the compositions resulting from the combination of the teachings of Dobrozsi, Maa, and Adjei, because it can be used to maintain the isotonicity of pharmaceutical formulations and it is the conjugate base of bitartrate. The combination of a weak acid (bitartrate) and its conjugate base (sodium tartrate) within the same formulation results in a buffer. Buffers are used to control pH. The control of pH is desirable to achieve pharmaceutically acceptable formulations. The use of a buffer to control pH provides an additional motivation for a person of ordinary skill in the art to make a composition comprising epinephrine bitartrate, leucine, and sodium tartrate that is pharmaceutically acceptable. A skilled artisan at the time of the instant invention would have known the desirability of administering a buffered formulation containing an epinephrine salt to a patient in need of said formulation.

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 140-143, 145, 151, 154, 159, and 160 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 10, 12, 14, 18, 25, and 27 of copending Application No. 10,818,902 in view of Maa et al. (U.S. patent 6,284,282).

Independent claim 140 of the instant application is drawn to a method for treating a patient in need of epinephrine comprising administering particles to the respiratory system of the patient, the particles comprising (i) epinephrine or a salt thereof (i.e. a therapeutic agent) and (ii) at least one pharmaceutically acceptable excipient, wherein the particles posses a fine particle fraction (FPF) of **less than** 5.6 μm of at least 45%.

Independent claim 1 of copending application '902 is drawn to a dry composition comprising spray dried particles for delivery a therapeutic agent to the deep lung, wherein the therapeutic agent and at least 55% of the particles have an aerodynamic diameter less than about 4.7 μm as measured by a Mark I Anderson Impactor for 30 seconds at 28.3 l/min flow rate. The instrument and flow rate used to measure the aerodynamic diameter of the therapeutic agents and particles in the composition of claim 1 of copending '902 is not given any weight in this analysis.

Maa defines FPF as powder with an aerodynamic mass median diameter of less than 6.8 μm. With regards to claim 140 of the instant application the FPF would be evaluated for particles having an aerodynamic mass median diameter of less than 5.6 μm.

The particles of copending application '902 have an aerodynamic diameter less than about 4.7 mm, which is less than 5.6 μm (μm is an accepted abbreviation for micron). The

limitation in claim 1 for the aerodynamic diameter of the particles is an upper size limit. Therefore the particles in claim 1 cannot mathematically have an average aerodynamic diameter that is greater than about 4.7 μm. In light of Maa's definition for FPF, the composition in claim 1 of copending application '902 would meet the FPF limitation of claim 140.

The term "therapeutic agent" of independent claim 1 of copending '902 encompasses epinephrine, which is a hormone used to treat anaphylaxis and other conditions. In addition, powdered epinephrine is taught in the specification of copending application '902. Therefore, it would be obvious to a person of ordinary skill in the art that the particles of '902 comprising a therapeutic agent that is epinephrine are similar to those particles used in the methods of treatment claimed in the instant application.

The use of the word "comprising" in claim 1 of copending application '902 allows for the inclusion of other ingredients in the composition, including pharmaceutically acceptable excipients. Claim 5 of '902 further limits claim 1 of the same application to include pharmaceutically acceptable excipients. Claim 9 limits the therapeutic agent to a group of drugs, including hormones. Epinephrine is a hormone.

Claims 1,5, and 9 of '902 are for compositions. Claims 140-143 of the instant application relate to methods of treatment, utilizing particles with limitations that encompass the compositions of claims 1, 5, and 9 of '902.

Independent claim 14 in '902 is for a method of delivering compositions comprising the particles of claim 1 of '902 to the respiratory tract. Delivering a composition comprising a therapeutic agent to a patient's respiratory tract is the same thing as administering said agent to the respiratory system, as the respiratory tract is part of the respiratory system.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Claims 140-173 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JHAA

Alton Pryor
Primary Examiner
A.U. 1616